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L5       49854 (VASCULAR DISEASE) (3A) (CEREBRAL OR BRAIN OR CNS OR
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=> s 20-HETE (8A) l5
L6          1 20-HETE (8A) L5

=> s l6 or l3
L7          12 L6 OR L3

=> d l7 bib ab

L7   ANSWER 1 OF 12     MEDLINE on STN
AN   2005316540     IN-PROCESS
DN   PubMed ID: 15831442
TI   Beneficial Effects of a New 20-Hydroxyeicosatetraenoic Acid
Synthesis
     Inhibitor, TS-011 [N-(3-Chloro-4-morpholin-4-yl)
Phenyl-N'-hydroxyimido
     Formamide], on Hemorrhagic and Ischemic Stroke.
AU   Miyata Noriyuki; Seki Takayuki; Tanaka Yu; Omura Tomohiro;
Taniguchi
     Kazuo; Doi Mariko; Bandou Kagumi; Kametani Shunichi; Sato
Masakazu;
     Okuyama Shigeru; Cambj-Sapunar Liana; Harder David R; Roman
Richard J
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CS Medicinal Pharmacology Laboratory, Medicinal Research Laboratories, Taisho
Pharmaceutical Co., Ltd, 1-403 Yoshino-cho, Kita-ku, Saitama-city, Saitama
331-9530, Japan.. noriyuki.miyata@po.rd.taisho.co.jp
SO Journal of pharmacology and experimental therapeutics, (2005 Jul) 314 (1)
77-85. Electronic Publication: 2005-04-14.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20050621
Last Updated on STN: 20050621
AB The present study characterized the effects of TS-011 [N-(3-chloro-4-
morpholin-4-yl) phenyl-N'-hydroxyimido formamide], a new selective
inhibitor of the synthesis of 20-hydroxyeicosatetraenoic acid (20-HETE),
on the metabolism of arachidonic acid by human and rat renal microsomes
and the inhibitory effects of this compound on hepatic cytochrome P450
enzymes involved in drug metabolism. The effects of TS-011 on the fall in
cerebral blood flow following subarachnoid hemorrhage (SAH) and in
reducing infarct size in ischemic **stroke** models were also
examined since **20-HETE** may contribute to the
development of cerebral vasospasm. TS-011 inhibited the synthesis of
20-HETE by human renal microsomes and recombinant CYP4A11 and 4F2, 4F3A,
and 4F3B enzymes with IC(50) values around 10 to 50 nM. It had no effect
on the activities of CYP1A, 2C9, 2C19, 2D6, or 3A4 enzymes. TS-011
inhibited the synthesis of 20-HETE by rat renal microsomes with an IC(50)
of 9.19 nM, and it had no effect on epoxygenase activity at a
concentration of 100 muM. TS-011 (0.01-1 mg/kg i.v.) reversed the fall in
cerebral blood flow and the increase in
20-HETE levels in the cerebrospinal fluid of rats after
SAH. TS-011 also reduced the infarct volume by 35% following transient
ischemic stroke and in intracerebral hemorrhage in rats. Injection of
20-HETE (8 or 12 mg/kg) into the carotid artery produced an infarct

similar to that seen in the ischemic stroke model. These studies indicate
that blockade of the synthesis of 20-HETE with TS-011 opposes cerebral
vasospasm following SAH and reduces infarct size in ischemic models of
stroke.

=> d l7 1-12 bib ab

L7 ANSWER 1 OF 12 MEDLINE on STN
AN 2005316540 IN-PROCESS
DN PubMed ID: 15831442
TI Beneficial Effects of a New 20-Hydroxyeicosatetraenoic Acid Synthesis
Inhibitor, TS-011 [N-(3-Chloro-4-morpholin-4-yl) Phenyl-N'-hydroxyimido
Formamide], on Hemorrhagic and Ischemic Stroke.
AU Miyata Noriyuki; Seki Takayuki; Tanaka Yu; Omura Tomohiro; Taniguchi
Kazuo; Doi Mariko; Bandou Kagumi; Kametani Shunichi; Sato Masakazu;
Okuyama Shigeru; Cambj-Sapunar Liana; Harder David R; Roman Richard J
CS Medicinal Pharmacology Laboratory, Medicinal Research Laboratories, Taisho
Pharmaceutical Co., Ltd, 1-403 Yoshino-cho, Kita-ku, Saitama-city, Saitama
331-9530, Japan.. noriyuki.miyata@po.rd.taisho.co.jp
SO Journal of pharmacology and experimental therapeutics, (2005 Jul) 314 (1)
77-85. Electronic Publication: 2005-04-14.
Journal code: 0376362. ISSN: 0022-3565.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS NONMEDLINE; IN-DATA-REVIEW; IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20050621
Last Updated on STN: 20050621
AB The present study characterized the effects of TS-011 [N-(3-chloro-4-
morpholin-4-yl) phenyl-N'-hydroxyimido formamide], a new selective
inhibitor of the synthesis of 20-hydroxyeicosatetraenoic acid (20-HETE),
on the metabolism of arachidonic acid by human and rat renal microsomes
and the inhibitory effects of this compound on hepatic cytochrome P450
enzymes involved in drug metabolism. The effects of TS-011 on the fall in

cerebral blood flow following subarachnoid hemorrhage (SAH) and in reducing infarct size in ischemic **stroke** models were also examined since **20-HETE** may contribute to the development of cerebral vasospasm. TS-011 inhibited the synthesis of 20-HETE by human renal microsomes and recombinant CYP4A11 and 4F2, 4F3A, and 4F3B enzymes with IC(50) values around 10 to 50 nM. It had no effect on the activities of CYP1A, 2C9, 2C19, 2D6, or 3A4 enzymes. TS-011 inhibited the synthesis of 20-HETE by rat renal microsomes with an IC(50) of 9.19 nM, and it had no effect on epoxygenase activity at a concentration of 100 muM. TS-011 (0.01-1 mg/kg i.v.) reversed the fall in **cerebral blood flow** and the increase in **20-HETE** levels in the cerebrospinal fluid of rats after SAH. TS-011 also reduced the infarct volume by 35% following transient ischemic stroke and in intracerebral hemorrhage in rats. Injection of 20-HETE (8 or 12 mg/kg) into the carotid artery produced an infarct similar to that seen in the ischemic stroke model. These studies indicate that blockade of the synthesis of 20-HETE with TS-011 opposes cerebral vasospasm following SAH and reduces infarct size in ischemic models of stroke.

L7 ANSWER 2 OF 12 MEDLINE on STN
AN 2004095449 MEDLINE
DN PubMed ID: 14985052
TI Effects of a 20-HETE antagonist and agonists on cerebral vascular tone.
AU Yu Ming; Cambj-Sapunar Liana; Kehl Franz; Maier Kristopher G; Takeuchi Kazuhiko; Miyata Noriyuki; Ishimoto Tsuyoshi; Reddy L Manmohan; Falck John R; Gebremedhin Debebe; Harder David R; Roman Richard J
CS Department of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA.
NC GM-31278 (NIGMS)
HL-29587 (NHLBI)
HL-36279 (NHLBI)
HL-59996 (NHLBI)
SO European journal of pharmacology, (2004 Feb 23) 486 (3) 297-306.

Journal code: 1254354. ISSN: 0014-2999.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200501
ED Entered STN: 20040302
Last Updated on STN: 20050105
Entered Medline: 20050104
AB This study examined the effects of a 20-hydroxyeicosatetraenoic acid (20-HETE) antagonist, 20-hydroxyeicosa-6(Z),15(Z)-dienoic acid (WIT002) and two agonists, 4-amino-N-(20-hydroxy-eicosa-5(Z),14(Z)-dienoyl) benzenesulfonamide (ABSA) and 20-hydroxyeicosa-5(Z),14(Z)-dienoic acid (WIT003), on the diameter of rat middle cerebral arteries in vitro and on cerebral blood flow in vivo. WIT003, ABSA and 20-HETE all had a similar effect to reduce the diameter of the middle cerebral artery by 26%. WIT003 and 20-HETE both increased intracellular Ca2+ concentration ([Ca2+]i) in vascular smooth muscle cells isolated from the middle cerebral artery. In contrast, WIT002 had no effect on the basal diameter of the middle cerebral artery but it attenuated the vasoconstrictor responses and the rise in [Ca2+]i in vascular smooth muscle cells following administration of 20-HETE and 5-hydroxytryptamine (5-HT). WIT003 partially restored the vasoconstrictor response to 5-HT in the middle cerebral artery after administration of an inhibitor of the endogenous synthesis of 20-HETE. Infusion of the 20-HETE agonists, WIT003 and ABSA, into cisterna magna of rats reduced baseline **cerebral blood flow** by 20%, whereas administration of the **20-HETE** antagonist, WIT002, had no effect. Intracisternal injection of WIT002 attenuated the fall in cerebral blood flow following injection of blood into the cisterna magna, whereas administration of the 20-HETE agonist, ABSA, potentiated this response. These findings indicate that the 20-HETE agonists, WIT003 and ABSA, increase cerebral vascular tone both in vivo and in vitro and suggest

blocking the vasoconstrictor actions of 20-HETE may be useful to prevent
the acute fall in cerebral blood flow following subarachnoid hemorrhage.

L7 ANSWER 3 OF 12 MEDLINE on STN
AN 2003209741 MEDLINE
DN PubMed ID: 12677022
TI Contribution of 5-hydroxytryptamine1B receptors and 20-hydroxyeiscosatetraenoic acid to fall in cerebral blood flow after subarachnoid hemorrhage.
AU Cambj-Sapunar Liana; Yu Ming; Harder David R; Roman Richard J
CS Department of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226, USA.
SO Stroke; a journal of cerebral circulation, (2003 May) 34 (5) 1269-75.
Electronic Publication: 2003-04-03.
Journal code: 0235266. ISSN: 1524-4628.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200306
ED Entered STN: 20030506
Last Updated on STN: 20030701
Entered Medline: 20030630
AB BACKGROUND AND PURPOSE: This study examined the interaction between 5-hydroxytryptamine1B (5-HT1B) receptors and 20-hydroxyeiscosatetraenoic acid (**20-HETE**) in contributing to the acute fall in regional **cerebral blood flow** (rCBF) after subarachnoid hemorrhage (SAH) in rats. METHODS: The effects of intracisternal injection of 0.3 mL of arterial blood, artificial cerebrospinal fluid, and 5-HT on rCBF and the levels of 20-HETE and 5-HT in cerebrospinal fluid were measured in rats pretreated with vehicle, a 5-HT1B receptor antagonist (isamoltane hemifumarate), or an inhibitor of the synthesis of 20-HETE (HET0016). The effects of HET0016 and isamoltane on the vasoconstrictor response and changes in [Ca2+]i to 5-HT were also studied in middle cerebral arteries and vascular smooth muscle cells isolated from these vessels. RESULTS: 20-HETE and 5-HT levels in cerebrospinal fluid rose from 172+/-10 to 629+/-44 ng/mL and from 6+/-4 to 1163+/-200 nmol/mL, respectively, after SAH. rCBF fell by 30% 10 minutes

after SAH, and it remained at this level for the next 2 hours. Blockade of 5-HT1B receptors prevented the sustained fall in rCBF seen after SAH. Intracisternal injection of 5-HT mimicked SAH by increasing 20-HETE levels in cerebrospinal fluid to 475+/-94 ng/mL and reducing rCBF by 30%. Blockade of the synthesis of 20-HETE with HET0016 prevented the fall in rCBF produced by 5-HT. Isamoltane and HET0016 reduced the vasoconstrictor response of isolated MCA to 5-HT by >60% and diminished the rise in [Ca2+]i produced by 5-HT in vascular smooth muscle cells isolated from these arteries. CONCLUSIONS: These results suggest that the release of 5-HT after SAH activates 5-HT1B receptors and the synthesis of 20-HETE and that 20-HETE contributes to the acute fall in rCBF by potentiating the vasoconstrictor response of cerebral vessels to 5-HT.

L7 ANSWER 4 OF 12 MEDLINE on STN
AN 2002161743 MEDLINE
DN PubMed ID: 11893593
TI **20-HETE** contributes to the acute fall in **cerebral blood flow** after subarachnoid hemorrhage in the rat.
AU Kehl Franz; Cambj-Sapunar Liana; Maier Kristopher G; Miyata Noriyuki; Kametani Shunishi; Okamoto Hirotsugu; Hudetz Anthony G; Schulte Marie L; Zagorac Drazen; Harder David R; Roman Richard J
CS Department of Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226, USA.
NC GM-56398 (NIGMS)
HL-10407-01 (NHLBI)
HL-29587 (NHLBI)
HL-29662 (NHLBI)
HL-59996 (NHLBI)
SO American journal of physiology. Heart and circulatory physiology, (2002 Apr) 282 (4) H1556-65.
Journal code: 100901228. ISSN: 0363-6135.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200205

ED Entered STN: 20020315
Last Updated on STN: 20020510
Entered Medline: 20020509

AB This study examined the effects of blocking the formation of 20-hydroxyeicosatetraenoic acid (**20-HETE**) on the acute fall in **cerebral blood flow** after subarachnoid hemorrhage (SAH) in the rat. In vehicle-treated rats, regional cerebral blood flow (rCBF) measured with laser-Doppler flowmetry fell by 30% 10 min after the injection of 0.3 ml of arterial blood into the cisterna magna, and it remained at this level for 2 h. Pretreatment with inhibitors of the formation of 20-HETE, 17-octadecynoic acid (17-ODYA; 1.5 nmol intrathecally) and N-hydroxy-N'-(4-butyl-2-methylphenyl)formamidine (HET0016; 10 mg/kg iv), reduced the initial fall in rCBF by 40%, and rCBF fully recovered 1 h after induction of SAH. The concentration of 20-HETE in the cerebrospinal fluid rose from 12 +/- 2 to 199 +/- 17 ng/ml after SAH in vehicle-treated rats. 20-HETE levels averaged only 15 +/- 11 and 39 +/- 13 ng/ml in rats pretreated with 17-ODYA or HET0016, respectively. HET0016 selectively inhibited the formation of 20-HETE in rat renal microsomes with an IC(50) of <15 nM and human recombinant CYP4A11, CYP4F2, and CYP4F3 enzymes with an IC(50) of 42, 125, and 100 nM, respectively. These results indicate that 20-HETE contributes to the acute fall in rCBF after SAH in rats.

L7 ANSWER 5 OF 12 MEDLINE on STN
AN 2000344722 MEDLINE
DN PubMed ID: 10884373
TI Production of **20-HETE** and its role in autoregulation of **cerebral blood flow.**
CM Comment in: Circ Res. 2000 Jul 7;87(1):4-5. PubMed ID: 10884363
AU Gebremedhin D; Lange A R; Lowry T F; Taheri M R; Birks E K; Hudetz A G; Narayanan J; Falck J R; Okamoto H; Roman R J; Nithipatikom K; Campbell W B; Harder D R
CS Cardiovascular Research Center, Department of Physiology, Medical College of Wisconsin, Milwaukee, WI, USA.
NC HL-33833 (NHLBI)
HL-51055 (NHLBI)

NS-32321 (NINDS)
+
SO Circulation research, (2000 Jul 7) 87 (1) 60-5.
Journal code: 0047103. ISSN: 0009-7330.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200008
ED Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000803
AB In the brain, pressure-induced myogenic constriction of cerebral arteriolar muscle contributes to autoregulation of cerebral blood flow (CBF). This study examined the role of 20-HETE in autoregulation of CBF in anesthetized rats. The expression of P-450 4A protein and mRNA was localized in isolated cerebral arteriolar muscle of rat by immunocytochemistry and in situ hybridization. The results of reverse transcriptase-polymerase chain reaction studies revealed that rat cerebral microvessels express cytochrome P-450 4A1, 4A2, 4A3, and 4A8 isoforms, some of which catalyze the formation of 20-HETE from arachidonic acid. Cerebral arterial microsomes incubated with [(14)C]arachidonic acid produced 20-HETE. An elevation in transmural pressure from 20 to 140 mm Hg increased 20-HETE concentration by 6-fold in cerebral arteries as measured by gas chromatography/mass spectrometry. In vivo, inhibition of vascular 20-HETE formation with N-methylsulfonyl-12, 12-dibromododec-11-enamide (DDMS), or its vasoconstrictor actions using 15-HETE or 20-hydroxyeicosa-6(Z),15(Z)-dienoic acid (20-HEDE), attenuated autoregulation of CBF to elevations of arterial pressure. In vitro application of DDMS, 15-HETE, or 20-HEDE eliminated pressure-induced constriction of rat middle cerebral arteries, and 20-HEDE and 15-HETE blocked the vasoconstriction action of 20-HETE. Taken together, these data suggest an important role for 20-HETE in the autoregulation of CBF.

L7 ANSWER 6 OF 12 EMBASE

on STN
AN 2002218815 EMBASE
TI **20-HETE** contributes to the acute fall in **cerebral blood flow** after subarachnoid hemorrhage in the rat.
AU Kehl F.; Cambj-Sapunar L.; Maier K.G.; Miyata N.; Kametani S.; Okamoto H.; Hudetz A.G.; Schulte M.L.; Zagorac D.; Harder D.R.; Roman R.J.
CS R.J. Roman, Dept. of Physiology, Medical College of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI 53226, United States. rroman@mcw.edu
SO American Journal of Physiology - Heart and Circulatory Physiology, (2002) Vol. 282, No. 4 51-4, pp. H1556-H1565.
Refs: 45
ISSN: 0363-6135 CODEN: AJPPDI
CY United States
DT Journal; Article
FS 002 Physiology
008 Neurology and Neurosurgery
LA English
SL English
ED Entered STN: 20020708
Last Updated on STN: 20020708
AB This study examined the effects of blocking the formation of 20-hydroxyeicosatetraenoic acid (**20-HETE**) on the acute fall in **cerebral blood flow** after subarachnoid hemorrhage (SAH) in the rat. In vehicle-treated rats, regional cerebral blood flow (rCBF) measured with laser-Doppler flowmetry fell by 30% 10 min after the injection of 0.3 ml of arterial blood into the cisterna magna, and it remained at this level for 2 h. Pretreatment with inhibitors of the formation of 20-HETE, 17-octadecynoic acid (17-ODYA; 1.5 nmol intrathecally) and N-hydroxy-N'-(4-butyl-2-methylphenyl)formamidine (HET0016; 10 mg/kg iv), reduced the initial fall in rCBF by 40%, and rCBF fully recovered 1 h after induction of SAH. The concentration of 20-HETE in the cerebrospinal fluid rose from 12 ± 2 to 199 ± 17 ng/ml after SAH in vehicle-treated rats. 20-HETE levels averaged only 15 ± 11 and 39 ± 13 ng/ml in rats pretreated with 17-ODYA or HET0016, respectively. HET0016 selectively inhibited the formation of 20-HETE in rat renal microsomes with an IC(50) of <15 nM and human recombinant CYP4A11, CYP4F2, and CYP4F3 enzymes with an IC(50) of

42, 125, and 100 nM, respectively. These results indicate that 20-HETE
contributes to the acute fall in rCBF after SAH in rats.

L7 ANSWER 7 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2004:221288 BIOSIS
DN PREV200400223384
TI Effect of TS-011, an inhibitor of the synthesis of **20-HETE**, on **cerebral blood flow** after
subarachnoid hemorrhage (SAH) in rats.
AU Miyata, Noriyuki [Reprint Author]; Seki, Takayuki [Reprint Author];
Taniguchi, Kazuo [Reprint Author]; Doi, Mariko [Reprint Author]; Omura,
Tomohiro [Reprint Author]; Bandou, Kagumi [Reprint Author]; Mano, Yoko
[Reprint Author]; Kametani, Shunichi [Reprint Author]; Ishii, Takaaki
[Reprint Author]; Amada, Hideaki [Reprint Author]; Kobayashi-Matsunaga,
Yuko [Reprint Author]; Sato, Masakazu [Reprint Author]; Tanaka, Makoto
[Reprint Author]; Okuyama, Shigeru [Reprint Author]; Cambj-Sapunar, Liana;
Roman, Richard J.; Harder, David R.
CS Med. Res. Labs., Taisho Pharmaceut. Co., Ltd., Saitama, 331-9530, Japan
SO Journal of Pharmacological Sciences, (2004) Vol. 94, No. Supplement 1, pp.
292P. print.
Meeting Info.: 77th Annual Meeting of the Japanese Pharmacological
Society. Osaka, Japan. March 08-10, 2004. Japanese Pharmacological
Society.
ISSN: 1347-8613 (ISSN print).
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 21 Apr 2004
Last Updated on STN: 21 Apr 2004

L7 ANSWER 8 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2004:204096 BIOSIS
DN PREV200400204639
TI Reduction of brain damage following focal cerebral ischemia by TS - 011, a
20 - hydroxyeicosatetraenoic acid synthesizing enzyme inhibitor.
AU Omura, T. [Reprint Author]; Miyata, N. [Reprint Author]; Tanaka, Y.

[Reprint Author]; Kitano, K. [Reprint Author]; Koizumi, C. [Reprint Author]; Fukawasa, M. [Reprint Author]; Endo, H. [Reprint Author]; Hachiuma, K. [Reprint Author]; Minagawa, T. [Reprint Author]; Sakurai, T. [Reprint Author]; Yoshida, S. [Reprint Author]; Okuyama, S. [Reprint Author]; Nakaike, S. [Reprint Author]; Roman, R. J.; Harder, D. R.

CS Dept of Physiology, Taisho Pharmaceut. Co., Ltd, Saitama, Japan

SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003) Vol. 2003, pp. Abstract No. 741.5. http://sfn.scholarone.com. e-file.

Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.

DT Conference; (Meeting) Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 14 Apr 2004 Last Updated on STN: 14 Apr 2004

AB 20-Hydroxyeicosatetraenoic acid (20-HETE) is one of the metabolites of arachidonic acid catalyzed by CYP4A isozymes. 20-HETE inhibits the large-conductance, Ca2+-activated K+-channel and increases Ca2+ influx through the voltage-gated Ca2+ channel. 20-HETE potently constricts cerebral arteries from a variety of species through these mechanisms. Recent studies have indicated that **20-HETE** contributes the acute fall in **cerebral blood flow** in rats following subarachnoid hemorrhage. Inhibition of 20-HETE formation might increase collateral blood flow and be useful in reducing brain damage following ischemic stroke as well. Recently, we developed the potent and selective inhibitor of 20-HETE synthesizing enzyme, TS-011. The present study examined the effects of TS-011 on infarct size following 1 hr of transient occlusion and 23 hr of reperfusion of the middle cerebral artery occlusion (MCAO) of rats. Plasma levels of 20-HETE increased significantly from 518 to 772 pg/mL 3 and 6 hours after occlusion and reperfuion of MCA. There was also upregulation of the

expression of CYP4A protein in the penumbra region of infarct area in
comparison to the contralateral hemisphere. Intravenous infusion of
TS-011 (0.1 mg/kg/hr) significantly reduced the infarct volume by 35%.
The reduction of infarct volume by TS-011 was even observed when the
compound was administered 4 hours after occlusion of the MCA. TS-011
prevented the increase in plasma 20-HETE levels following occlusion and
reperfusion of the MCA. TS-011 also reduced the infarct volume by 30 % in
a photochemically-induced model of permanent MCAO of rats. These results
suggest that inhibition of the production of **20-HETE**
with TS-011 provides neuroprotection following ischemic **stroke**.

L7 ANSWER 9 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2004:204095 BIOSIS
DN PREV200400204638
TI An inhibitor of the synthesis of **20** - **HETE**, TS - 011
blocks the fall in **cerebral blood flow** after
subarachnoid hemorrhage (SAH) in rats.
AU Miyata, N. [Reprint Author]; Seki, T. [Reprint Author]; Taniguchi, K.
[Reprint Author]; Doi, M. [Reprint Author]; Bando, K. [Reprint Author];
Mano, Y. [Reprint Author]; Kametani, S. [Reprint Author]; Okuyama, S.
[Reprint Author]; Ishii, T. [Reprint Author]; Amada, H. [Reprint Author];
Kobayashi-Matsunaga, Y. [Reprint Author]; Sato, M. [Reprint Author];
Tanaka, M. [Reprint Author]; Cambj-Sapunar, L.; Roman, R. J.; Harder, D.
R.
CS Medicinal Res. Labs., Taisho Pharmaceut. Co., Ltd., Saitama-city, Japan
SO Society for Neuroscience Abstract Viewer and Itinerary Planner, (2003)
Vol. 2003, pp. Abstract No. 741.4. http://sfn.scholarone.com. e-file.
Meeting Info.: 33rd Annual Meeting of the Society of Neuroscience. New
Orleans, LA, USA. November 08-12, 2003. Society of Neuroscience.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 14 Apr 2004

Last Updated on STN: 14 Apr 2004
AB This study examined the effects of TS-011 on the metabolism of arachidonic acid. TS-011 selectively inhibited the formation of 20-hydroxy-5,8,11,14 eicosatetraenoic acid (20-HETE) in rat renal microsomes. The IC50 values averaged 41.9 + 11.3 nM and it had no effect on the synthesis of epoxyeicosatrienoic acids, cycloxygenase I and II at concentrations up to 1000 nM. In human renal microsomes, TS-011 potently inhibited the formation of 20-HETE with IC50 value of 8.7 + 1.8 nM. TS-011 also inhibited the production of 20-HETE by human recombinant CYP4F2, CYP4F3A, CYP4F3B and CYP4A11 with IC50 values of 30.9 +1.7 nM, 32.7 + 4.7nM, 56.0 + 5.6nM and 135 + 6.7nM, respectively. TS-011 has no effect on the activities of the major human drug metabolizing enzymes, CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 a concentration of 1000 nM. In vehicle treated rats, regional cerebral blood flow (rCBF) measured with laser-Doppler flowmetry fell by 30 %, 10 min after induction of SAH by injecting of 0.3 ml of arterial blood into the cisterna magna, and it remained at this level for 2 hr. Pretreament with TS-011 (0.1 mg/kg) reduced the acute fall in rCBF after SAH by 40% and rCBF fully recovered to control within 2hr. TS-011 also completely reversed the fall in CBF when given 30 minutes after induction of SAH. The concentration of 20-HETE in the cerebrospinal fluid rose from 40 to 620 ng/ml after SAH in vehicle treated rats. 20-HETE levels were significantly reduced to 350 ng/ml after SAH in rats treated with TS-011 (0.1 mg/kg). These results indicate that TS-011 is a potent and selective inhibitor of the synthesis of **20-HETE** and it reverses the fall in acute **cerebral blood flow** after SAH in rats.

L7 ANSWER 10 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AN 2003:89980 BIOSIS
DN PREV200300089980

TI An Inhibitor of **20-HETE** Formation Attenuates the Fall in **Cerebral Blood Flow** Following Subarachnoid Hemorrhage.

AU Okamoto, Hirotsugu [Reprint Author]; Maier, Kristopher G. [Reprint Author]; Harder, David R. [Reprint Author]; Roman, Richard J. [Reprint Author]

CS Physiology, Medical College of Wisconsin, Milwaukee, WI, USA

SO Anesthesiology Abstracts of Scientific Papers Annual Meeting, (2002) No. 2000, pp. Abstract No. 736. http://www.asa-abstracts.com. cd-rom.

Meeting Info.: 2000 Annual Meeting of the American Society of Anesthesiologists. San Francisco, CA, USA. October 16-18, 2000. American Society of Anesthesiologists Inc.

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LA English

ED Entered STN: 12 Feb 2003
Last Updated on STN: 12 Feb 2003

AB INTRODUCTION: Acute cerebral vasospasm following subarachnoid hemorrhage (SAH) causes ischemic stroke. Although endothelin, nitric oxide and thromboxane have been implicated to play a role in cerebral vasospasm, the relative importance of these mediators versus others have not been fully resolved. Recently, a cytochrome P450 metabolite of arachidonic acid, 20-hydroxyeicosatetraenoic acid (20-HETE)(a potent vasoconstrictor), has been reported to play a pivotal role in the regulation of cerebrovascular tone. To examine the role of **20-HETE** in mediating acute cerebral vasospasm, we compared **cerebral blood flow** responses following SAH in rats treated with vehicle or an inhibitor of 20-HETE formation,17-ODYA. METHODS: Experiments were performed on ketamine and thiobutabarbiturate anesthetized male Sprague-Dawley rats weighing 250-300 g. The animals were artificially ventilated and arterial pressure and PCO2 levels were monitored. Regional cerebral blood flow (rCBF) was continuously measured with laser-Doppler flowmetry through thin closed cranial window over the parietal region of the cerebral cortex. SAH was induced by injecting 0.3 ml of arterial

blood into the Cisterna Magna. 20-HETE levels were measured by fluorescent HPLC from samples drawn via Cisterna Magna before and after SAH. Rats were divided into two groups. In group 1 (n=7), rats were given an injection of 2 nmoles of 17-ODYA into the Cisterna Magna 1 hour prior to SAH. In group 2 (n=5), rats received vehicle. Data was expressed mean +-SEM and significance of differences was determined using ANOVA followed by a Duncan's test. RESULTS: In vehicle-treated rats, rCBF fell by 40% within 10 minutes after SAH, and it remained at this level for the 2 hour duration of the experiment. In contrast, the initial decrease in rCBF was significantly less in the rats pretreated with 17-ODYA, and rCBF returned to pre-SAH levels within 2 hours (See Figure). In vehicle-treated rats, 20-HETE levels in cerebrospinal fluid (CSF) increased significantly from 7.5+-4 ng/ml to 204+-13 ng/ml after injection of blood; while 20-HETE levels did not increase in the 17-ODYA treated rats. CONCLUSIONS: These results indicate that SAH markedly increased 20-HETE levels in CSF, and 17-ODYA prevented both the increase of 20-HETE levels and the fall in rCBF following SAH. 20-HETE, a cytochrome P450 metabolite of arachidonic acid, may contribute to acute cerebral vasospasm following SAH. Preventing the production of, or the actions of 20-HETE, after SAH may provide a new therapeutic approach for the treatment of SAH and cerebral vasospasm.

L7 ANSWER 11 OF 12 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AN 2002:354570 BIOSIS

DN PREV200200354570

TI The **20-HETE** antagonist WIT-002 attenuates the acute reduction of **cerebral blood flow** after subarachnoid hemorrhage (SAH) in the rat.

AU Kehl, Franz [Reprint author]; Maier, Kristopher G. [Reprint author]; Miyata, Noriyuki; Kametani, Shunishi; Falck, John R.; Harder, David R.;

Roman, Richard J. [Reprint author]
CS Physiology, Medical College of Wisconsin, 8701 Watertown Plank Rd,
Milwaukee, WI, 53226, USA
SO FASEB Journal, (March 22, 2002) Vol. 16, No. 5, pp. A845. print.
Meeting Info.: Annual Meeting of Professional Research Scientists on
Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002.
CODEN: FAJOEC. ISSN: 0892-6638.
DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 26 Jun 2002
Last Updated on STN: 26 Jun 2002
AB The effects of the 20-hydroxyeicosatetraenoic acid (20-HETE) agonist,
4-amino-N-(hydroxy-eicosa-5,14-dienoyl)-benzenesulfonamide (JYII16925),
and of the antagonist, 20-hydroxyeicosa-6(Z), 15(Z)- dienoic acid
(WIT-002) on regional cortical cerebral blood flow (rCBF), following SAH
in the rat, were examined. SAH was induced by injection of 0.3 ml of
blood into the Cisterna Magna and rCBF was measured by laser Doppler
flowmetry. In vehicle treated rats (n=6) SAH produced a fall of rCBF to
65% of baseline value and remained at this level throughout the
experiment. Pretreatment of the rats with WIT-002 (1.5 nM, intrathecally;
n=7) ameliorated the fall in rCBF at 10 min by 40% and rCBF recovered to
baseline values (93+-3% at 120 min). Pretreatment of the rats with
JYII16925 (1.5 nM, intrathecally; n=6) aggravated the fall in rCBF after
SAH and lowered rCBF compared to vehicle treated rats by an additional
35%. The concentration of 20-HETE in CSF averaged 63+-5, 286+-11,
401+-239, and 430+-223 ng/ml, in sham-operated rats and rats treated prior
to SAH with vehicle, WIT-002, or JYII16925, respectively. These results
indicate that 20-HETE contributes to the acute fall in rCBF after SAH in
rats in vivo.

L7 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:353270 CAPLUS
DN 136:363861

TI Use of **20-HETE** synthesizing enzyme inhibitors as therapy for **cerebral vascular diseases**

IN Roman, Richard J.; Harder, David R.; Miyata, Noriyuki; Sato, Masakazu; Kameo, Kazuya; Okuyama, Shigeru

PA MCW Research Foundation, Inc., USA; Taisho Pharmaceutical Co., Ltd.

SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002036108	A2	20020510	WO 2001-US27605	20010906
WO 2002036108	A3	20021017		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2427557	AA	20020510	CA 2001-2427557	20010906
AU 2001088798	A5	20020515	AU 2001-88798	20010906
EP 1330240	A2	20030730	EP 2001-968558	20010906
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004512361	T2	20040422	JP 2002-538920	20010906

PRAI US 2000-245638P P 20001103
WO 2001-US27605 W 20010906

AB A method for treating cerebral vascular diseases in a human or non-human

animal is disclosed. The method involves inhibiting 20-HETE synthesizing enzyme activity sufficiently to increase or prevent a decrease in cerebral blood flow in the human or non-human animal.

=> file stnguide

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	80.87	81.08

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-0.73	-0.73

FILE 'STNGUIDE' ENTERED AT 13:00:58 ON 07 JUL 2005

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Jul 1, 2005 (20050701/UP).